

Nanotechnology in oral cancer: A comprehensive review

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Abstract

Oral health could be maintained by application of this technology in prevention, diagnosis and treatment. Oral cancer is a debilitating disease, and numerous research activities are being pursued worldwide to combat this deleterious process. Nanotechnology is very diverse field that has revolutionized the industry and is setting new trends in the management of oral cancer. Hence, we performed a PubMed search on nanotechnology in oral cancer and found 211 articles related to this search. We have reviewed the reported literature to the best of our abilities and summarized the various aspects of nanotechnology, its role in diagnosis - nanodiagnostics and treatment of oral cancer - nanotherapeutics in this article.

Keywords: Diagnosis, nanotechnology, oral cancer, therapy

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INTRODUCTION

Nanotechnology is the manipulation of matter on the molecular and atomic levels.^[1] It has been considered as multidisciplinary field of scientific research about different types of nanoparticles (NPs) as well as the application of new nanomaterials and nanodevices in numerous areas of human interest.^[2]

The concept of nanotechnology was elaborated by Richard P Feynman in 1959. The term nanotechnology was first defined by Norio Taniguchi of the Tokyo Science University in a 1974 paper as follows: "Nanotechnology" mainly consists of the processing of, separation, consolidation and deformation of materials by one atom or one molecule. It was popularized by K. Eric Drexler. One nanometer is one billionth, or 10^9 , of a meter.^[3]

In nanotechnology, we look for ways to use microscopic devices to perform tasks that are being done by hand or with equipment. Tiny machines, known as nanoassemblers, could be controlled by computer to perform specialized jobs. The nanoassemblers could be smaller than a cell nucleus so that they could fit into places that are hard to reach by hand or with other technology.^[4]

Application of nanotechnology is revolutionizing biomedical engineering by allowing new types of drug delivery, synthesis of tissue modules, development of biomaterial and improved surfaces for medical devices, *in vitro in vivo* methodologies, biofiltration systems and robotic assembly, among many other exciting advances.^[5]

Studying dental structures and surfaces from a nanoscale prospective leads to a better understanding of the structure function-physiological relationship of dental

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surfaces.^[5] In particular, diseases such as dental caries, tooth hypersensitivity and oral cancer can be quantified based on morphological, biophysical and biochemical nanoscale properties of tooth surface itself and dental materials or oral fluids such as saliva. Nanotechnology offers a broad range of innovations and improvement in prevention, diagnostics and treatment of oral diseases.^[6,7]

Nanomaterials are those materials with components <100 nm in at least one dimension. It includes atoms clusters, grains, fibers, films, nanoholes and composites form these combinations. The Various generations and constituents of nanotechnology is tabulated in Table 1. Its contents are modified from Ravisankar MS *et al.*^[8]

NANOMATERIALS

Nanomaterials in one dimension are termed as sheets, in two dimensions as nanowires, nanotubes and as quantum dots in three dimensions. Their properties vary from other materials due to two reasons - the increase in surface area and quantum effects. Nanomaterials due to their small size have a much-increased surface area per unit mass compared to bigger particles. All properties, including electrical, optical and magnetic ones, are altered.^[1]

Nanotechnology has applications in many fields such as medicine and dentistry.^[1]

APPROACHES TO NANODENTISTRY

Table 2 depicts the various approached to create nanostructures. Its contents are modified from Kaur J *et al.*^[9]

Bottom-Up approaches:

- Assembly of small components into compound structures.

Top-Down approaches:

- Creation of small structures using bigger ones in guiding their assembly.^[9]

DIAGNOSIS OF ORAL CANCER

Oral cancer (oral cavity and oropharynx) is a common and aggressive cancer that invades local tissue, can cause metastasis and has a high mortality rate.^[10]

Head and neck squamous cell carcinoma rank the sixth most common cancer in the world, and the survival rate has not improved significantly in the past 20 years despite the countless studies on this malignancy.^[11] Oral cancer is often diagnosed only after it has advanced to an untreatable stage^[12,13] where

Table 1: Generations of nanotechnology

Generation	Constituents
First generation: Passive nanostructures	Dispersed and contact nanostructures Aerosols Colloids Products incorporating nanostructures Coatings Polymers Ceramics Nanostructure metals Nanoparticle reinforced composites
Second generation: Active nanostructures	Bioactive, health effects-targeted drugs Bio-devices Physicochemical active structures Amplifiers Actuators Adaptive structures 3D transistors
Third generation: Nanosystems	Guided assembling of structures 3D networking of structures New hierarchical architectures Robotics Evolutionary systems
Fourth generation: Molecular nanosystems	Molecular devices by design Molecular devices by Atomic designing Molecular devices with emerging functions

Content of this table is modified from Ravisankar *et al.*^[8] 3D: Three-dimensional

Table 2: Depicting the various approaches to create nanostructures^[9]

Bottom-up approaches	Top-down approaches
Local anesthesia	Nano-composites
Hypersensitivity cure	Nano-impression materials
Tooth repositioning	Nano-solutions
Nano-robotic dentifrice (dentifrobots)	Nano-encapsulation
Dental durability and cosmetics	Nano-needles
Orthodontic treatment	Bone substitutes
Nano-diagnostics (photosensitizers and carriers)	Implants
Nano-therapeutics/drug delivery	Surface disinfectant
Bionic mandible	Decay resistant tooth
Skin grafts	Salivary diagnostics

the cancer cells have become aggressive and immune to therapeutic drugs. Detecting oral cancer at its earliest is thus vital for improving the survival rate of this disease.^[14]

The role of nanotechnology in oral cancer were searched in PubMed database using (“nanotechnology” [MeSH terms] or “nanotechnology” [all fields]) and (“mouth neoplasms” [MeSH terms] or (“mouth” [all fields] and “neoplasms” [all fields]) or “mouth neoplasms” [all fields] or (“oral” [All Fields] and “cancer” [all fields]) or “oral cancer” [all fields]). We found a total of 211 related articles. We have summarized the findings of various modes of nanotechnology used in diagnosis, therapy and follow-up of oral cancer in Table 3.^[15-30]

We have made a novel attempt to group them into separate sections including nanodiagnostics with tumor biomarkers and nanotherapeutics with drug-based delivery systems.

Table 3: The various implications of nanotechnology in oral cancer

Author	Work	Mode used
Gharat 2016 et al. ^[15]	They highlighted the etiology, line of the treatment and chemopreventive measures related to OSCC. They focused on data available in the research carried out worldwide in past 15 years related to the management of OSCC	Nanotechnology-based carrier systems
Gupta et al., 2017 ^[16]	Cytotoxic study showed that Ag ₅ -ZnO NCs kill oral carcinoma (KB) cells under visible light irradiation, and work as photosensitizers toward the PDT of cancer due to the excellent photocatalytic activity	Ag ₅ -ZnO NCs
Lollo et al., 2017 ^[17]	Investigated the potential of nanocarriers for oral delivery of peptide anticancer drugs. Results suggest that elisidepsin can be effectively loaded into the nanocapsules by adjusting the formulation parameters, using a solvent displacement technique	Nanocarriers
Ho 2016 et al. ^[18]	Assessed how the impact of nanotechnology in the clinic can be optimized through systematically designed combinatorial nanotherapy. In addition, they provided a clinical perspective on how a recently unveiled technology platform can substantially alter the landscape of combinatorial nanomedicine, drug development, as well as conventional drug development	Combinational nanotherapy
Rahimi 2016 et al. ^[19]	Bibliographical searches were performed using MEDLINE/ScienceDirect/OVID up to February 2015 using the following keywords (all fields): (“Curcumin” or “Curcuma longa”) and ([nanoparticles]) or (nanomicelles) or (microemulsions) or (liposome) or (phospholipid). These studies indicated that nanotechnology can formulate curcumin effectively, and this nano-formulated curcumin with a potent ability against various cancer cells were represented to have better efficacy and bioavailability under <i>in vivo</i> conditions	Nano-formulated curcumin
Jain and Jain 2016 ^[20]	Different categories of oral anticancer prodrugs along with recent clinical studies have been comprehensively reviewed here. Furthermore, novel anticancer prodrugs such as polymer-prodrugs and lipid-prodrugs have been discussed in detail. Finally, various nanocarrier-based approaches employed for oral delivery of anticancer prodrugs have also been discussed	Nanocarriers
Chu et al. 2016 ^[21]	Demonstrated effective inactivation of oral cancer cells through a combination of PTT and PDT effects based on LSPR around 1064 nm in wavelength of an NRI under femtosecond laser illumination	Au nano-ring
Nam et al., 2016 ^[22]	Tried to summarize various methods utilized for nanofabrication of quercetin formulations and stable and sustained delivery of quercetin. They have also highlighted the various desirable measures for its use as a promising onco-therapeutic agent	Nanofabrication of quercetin formulations
Lucky et al., 2016 ^[23]	Their work, one of the longest study till date in terms of safety (120 days), PDT efficacy (35 days) and survival (60 days), demonstrated the usefulness of UCN based PDT technology for targeted treatment of thick and bulky head and neck tumors	Upconversion nanoparticle
Ankri et al., 2016 ^[24]	The airSEM pictures presented a gradient of GNRs from the tumor to normal epithelium, spread in an area of 1 mm, suggesting tumor margins of 1 mm. DR measurements, performed in a resolution of 1 mm, of human oral SCC have shown a clear difference between the DR profiles of the healthy epithelium and the tumor itself	Gold nanorods
Yen et al., 2016 ^[25]	Proposed a chemopreventive nanodiamond platform for the delivery of celecoxib (celebrex) to oral cancer lesions. This innovative platform allows for sustained drug release under physiological conditions, potentially enhancing chemopreventive efficacy of celecoxib without the physical and toxicological damage associated with conventional means of drug delivery	Chemopreventive nanodiamond platform
Masloub et al., 2016 ^[26]	Concluded that Curcumin nanoparticles could be more active in inducing apoptosis in short-term assays (24 h) than long-term assays (48 h) due to differential cellular uptake. While 5-FU nanoparticles induced higher significant apoptosis in long-term (48 h) compared to curcumin group	Curcumin nanoparticles
Mohan et al., 2016 ^[27]	Described the development and characterization of a PEGylated liposomal nanocarrier encapsulated with trans-resveratrol, a plant stilbenoid and Dox, a standard chemotherapeutic agent for treatment of oral squamous cell carcinoma	Nanocarriers
Saxena et al., 2015 ^[28]	Briefly described the architecture of the nanorobots and their role in oncotherapy. Robots will augment the surgeon's motor performance, diagnostic capability and sensations with haptics and augmented reality	Nanorobots
Ho et al., 2015 ^[29]	Reviewed various nanomaterials and the use of PPM-DD to optimize the efficacy and safety of current and future cancer treatment. How this platform can accelerate combinatorial nanomedicine and the broader pharmaceutical industry toward unprecedented clinical impact will also be discussed	Nanoparticles and combinatorial nanomedicine
Zhao et al., 2015 ^[30]	Suggested that when loaded with SNNP, 5-FU has better antitumor efficacy and lower side effects, indicating that SNNP can efficiently act as a readily accessible, robust, biocompatible and low-toxic nanobiomaterial which may find wide therapeutic applications clinically in the future	Nanoparticles

OSCC: Oral SCC, SNNP: Self-assembled nucleoside nanoparticle, 5-FU: 5-fluorouracile, PPM-DD: Phenotypic personalized medicine-drug development, Dox: Doxorubicin hydrochloride, PTT: Photothermal therapy, PDT: Photodynamic therapy, LSPR: Localized surface plasmon resonance, NRI: Au nanoring, UCN: Upconversion nanoparticle, AirSEM: Air scanning electron microscopy, GNRs: Gold nanorods, DR: Diffusion reflection, SCC: Squamous cell carcinoma

NANODIAGNOSTICS

It can be defined as the use of nanotechnology for clinical diagnostic purposes developed to meet the demands for increased sensitivity and earlier detection of disease. Nanotechnology has revolutionized cancer detection and treatment. It has the capability to detect even a single cancerous cell *in vivo* and deliver the highly toxic drugs directly to the cancerous cells. Nanoshells, carbon nanotubes, quantum dots,

supermagnetic NPs, nanowires, nanodiamonds, dendrimers and recently synthesized nanosponges are some of the materials used for cancer detection.^[31]

Using specific crosslinkers such as specific antibodies against cancer cells, individual cancer cells can be located. A novel set of lipid-coated; targeted quantum dots could be used for quantifying multiple specific biomarkers on the surfaces of individual cancer cells.^[31]

- Nanoscale cantilevers: Elastic beams used to attach with cancer-linked molecules^[1]
- Cantilever array sensors: Ultrasensitive mass detection technology^[32]
- Nanopores: Small holes that enable DNA passage one strand at a time, thus making DNA sequencing highly efficient
- Nanotubes: Carbon rods that can detect affected genes and also localize their location
- Quantum dots: These glow very brightly in ultraviolet light. They attach to proteins associated with cancer cells, thus localizing tumors^[1]
- Nanoelectromechanical Systems: Convert biochemical to electric signal
- Multiplexing modality: Sensing large numbers of different biomolecules simultaneously.^[32]

NPs can selectively target cancer biomarkers and cancer cells, allowing more sensitive diagnosis; early detection requiring minimal amount of tissue, monitoring of the progress of therapy and tumor burden over time, and destruction of solely the cancer cells. Plasmonic NPs conjugated to nuclear targeting peptides cause DNA damage and apoptotic populations in cancer cells.^[33] These NPs specifically target tumor cells, resulting in minimal damage to healthy tissues.

Basic knowledge of cell biology, tumor biology and immunology is essential to the rational design of NPs for cancer therapeutics, and advancement in nanotechnology will be critically dependent on the advancements made in cancer biology.^[31]

NANOMATERIALS FOR CANCER DIAGNOSIS

Prevention is the best cure for cancer. Early detection will greatly increase survival rates. An *in situ* tumor will be easier to eradicate than one that has metastasized. Different kinds of NPs are suitable for drug and gene delivery, probing DNA structures, etc., They include:

- Liposomes
- Polymeric NPs (Nanospheres and Nanocapsules)
- Solid lipid particles
- Nanocrystals
- Polymer Therapeutics such as dendrimers, fullerenes.
- Inorganic NPs (e.g. Gold and Magnetic Nanoparticles).^[34]

Kah *et al.*^[35] carried out a study which demonstrated the potential of antibody conjugated gold NPs to target and illuminate cancer cells under a reflectance-based optical imaging system. In particular, they have shown that gold NPs can provide an optical contrast to discriminate

between cancerous and normal cells and their conjugation with antibodies also allows them to map the expression of relevant biomarkers for molecular imaging.

NANOPARTICLES AS TUMOR BIOMARKERS

In vitro

NPs can be used for qualitative or quantitative *in vitro* detection of tumor cells. They help the detection process by concentrating and protecting a marker from degradation, to render the analysis more sensitive. Another approach was the encapsulation of inorganic biomarkers, rather than fluorescent organic markers. These compounds were more photostable and not hampered by the intrinsic fluorescence (background signal) emitted by cells and tissues, which makes them more suitable and sensitive for qualitative and especially quantitative detection.^[36]

In vivo

The physicochemical characteristics (particle size, surface charge, surface coating and stability) of the NPs allow the redirection and the concentration of the marker at the site of interest. Labeled colloidal particles could be used as radio diagnostic agents. On the other hand, some nonlabeled colloidal systems are already in use, and some are still being tested as contrast agents in diagnosis procedures such as computed tomography and nuclear magnetic resonance imaging.^[36]

Treatment of oral cancer

- Nanomaterials for brachytherapy: BrachySilTM
- Nanovectors for gene therapy
- Nonviral gene delivery systems^[1]
- Drug delivery across the blood-brain barrier.^[32]

Nanotechnology is probably the only method that can be used for site-specific action without causing side effects by killing the normal cells. Cancer nanotechnology is the latest trend in cancer therapy. It represents a great hope for improving cancer treatments by acting at least at two main levels: conferring new properties to a pharmaceutical agent (increased stability, modified pharmacokinetics, decreased toxicity, etc.) and targeting the agent directly to the tumor.^[37] A strategy could be to associate antitumor drugs with colloidal NPs, with the aim to overcome noncellular and cellular-based mechanisms of resistance and to increase the selectivity of drugs toward cancer cells while reducing their toxicity toward normal tissues.^[36]

NPs can serve as customizable, targeted drug delivery vehicles capable of ferrying chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells. This may allow for smaller doses of toxic substances

as the drugs are delivered directly to the target tissue. Some nanoscale delivery devices, such as dendrimers (spherical, branched polymers), silica-coated micelles, ceramic NPs and cross-linked liposomes can be targeted to cancer cells. This increases the selectivity of drugs toward cancer cells and will reduce the toxicity to normal tissue. This is done by attaching monoclonal antibodies or cell surface receptor ligands that bind specifically to the cancer cells.^[38]

Surface modification of NPs can also enhance the permeability of drugs and gives an option to create high-permeability NP-based cancer therapeutics. Research on the covalent attachment of peptidic membrane-translocation sequences has helped this concept. With improved cell permeability, NPs can become more therapeutically effective drug transport vehicles.^[38]

NPs have size of 5 nm to 200 nm, allowing their unique interaction with biological systems at the molecular level. As a result of their composition, NPs are capable of self-assembly and maintaining stability and specificity which are crucial to drug encapsulation and biocompatibility.^[34]

Combinatorial chemotherapy coupled with nanomedicine has opened a new horizon to the current therapeutic approaches that have failed due to tumor cell resistance and unwanted toxicity to normal cells. However, aggressive advances could be made when nano-based drug delivery systems paired with combination chemotherapeutic agents.^[39,40] Doxorubicin encapsulated or conjugated with divergent nanocarriers to enhance its specificity on targeting the cancerous cells DOX-nanocarrier complex attached to specific antibodies such as folate receptors or epidermal growth factor receptor which is abundantly expressed on the surface of cancerous cells. Both oral and intravenous formulation of doxorubicin are available.^[41]

Apoptotic effects on cancer cells were demonstrated following topical administration of 5-fluorouracil matrix tablets on a three dimensional outgrowth model of oral squamous cell carcinoma (OSCC); indicating that locoregional chemotherapy of OSCC could be effective. It has been successfully shown that modified chitosan NPs loaded with 5-aminolevulinic acid were taken up by oral cancer cells through folate receptor-mediated endocytosis.^[42]

NANOTECHNOLOGY BASED DRUG DELIVERY SYSTEMS

Nanoparticles

NPs can improve the stability of drugs and control their targeted delivery, allowing for a constant and uniform

concentration at the site of a lesion and facilitating drug extravasation into the tumor system, thus reducing side effects.^[43]

Newer PNPs were fabricated from polysaccharides, proteins and biocompatible/biodegradable polymers, such as polyethylene glycol (PEG), poly (γ -benzyl l-glutamate), poly-D, L-lactide, polylactic acid, poly D, L-glycolide, polylactide-co-glycolide, polycyanoacrylate, chitosan, gelatin and sodium alginate. They demonstrated physical stability, protection of incorporated labile drugs from degradation, controlled release and excellent tolerability; thus, they can be used for different routes of administration, such as parenteral, oral, dermal, ocular, pulmonary and rectal.^[44-46]

Liposomes

Liposomes have been intensively studied for the delivery of chemotherapeutic drugs to improve therapeutic efficacy and decrease the toxicity to normal cells. Liposome-based formulations for gene therapy, such as synthetic cationic liposomal-DNA called lipoplexes, have clear potential, particularly for oral cancer treatment.^[10]

Hydrogels

A hydrogel is a mesh of hydrophilic polymeric chains dispersed in water that could swell and release drugs for dissolution and disintegration through the spaces in their mesh. Hydrogels are attractive for oral administration because their polymeric chains can closely interact with saliva glycoproteins, causing a mucoadhesion phenomenon. There has been a great deal of interest in the use of hydrogels as chemotherapeutic drug delivery systems for drugs including paclitaxel, doxorubicin, DTX, tamoxifen and cisplatin.^[10] It is reported that the SAHA-cisplatin/PECE hydrogel system with direct intratumoral injections may be a useful method for the treatment of oral cancer and other solid tumors.^[47]

Liquid crystals

Liquid crystals (LCs) are a material in a differential state, demonstrating a property between a solid and a liquid. This state is called mesophase: the prefix “meso-” means “intermediate.” The LC systems significantly change the drug release profile and reduce the toxicity of drugs, improving clinical efficiency. LCs may be a promising strategy for the treatment of cancers, including oral cancer.^[10]

Layered nanoemulsions as mucoadhesive buccal systems:

The ability to rationally assess and control interfacial properties of chito-layered nanoemulsion systems permit

superior drug-loaded droplet designs with improved stability and added mucoadhesive functional performance. Encouraging data from new mucoadhesive buccal sprays and lozenges suggest the potential of such platforms to be used as adjuvant therapy for oral cancer patients. A chief aim would be to eliminate any residual cancerous cells remaining after tumor removal, hence preventing postsurgical tumor recurrence or risk of postoperative metastasis of residual detached cancerous cells.^[48]

In general, conventional chemotherapeutic drugs exhibit poor systemic stability, limited water solubility, unwanted drug-related side effects (bone marrow depression and nephrotoxicity) and relatively short half-life that prevent their further clinical application. Cis-Diamine-dichloro-platinum (cisplatin, CDDP) is one such drug which is extensively used for the treatment of various cancers such as ovarian, testicular, colorectal and oral squamous cancers, however, it suffers from many serious side effects. Studies have shown that nanocarriers caused better selective accumulation of CDDP in tumors while lessening its distribution in normal tissue. Therefore, biodegradable polymer, poly (lactic-co-glycolic acid) PEG (PLGA-PEG)-based self-assembled polymeric micelles was designed in a study conducted by Wang *et al.*,^[49] The hydrophilic poly (ethylene glycol) shell layer enables the particles to circulate for long time in the blood compartment which will facilitate its preferential accumulation in the tumor tissues.^[49]

PHYSICOCHEMICAL CHARACTERIZATION OF NANOPARTICLES

The CDDP-loaded PLGA NPs were formed by the self-assembly of drug in the hydrophobic core of the polymeric micelles. After being dissolved in DMSO and dialyzed against water, CDDP was able to spontaneously self-assemble into micelles with hydrophobic PLGA core and hydrophilic PEG outer shell. The resulting NPs were expected to be nanometer range. The particle size and size distributions of NP were evaluate by dynamic light scattering technique. The average size of drug-loaded PLGA NP was around ~100 nm while a slight increment in size was observed for PLGA/NR7 NP (~135 nm). It has been reported that micelles with an average size between 50- and 150-nm diameter ranges, could easily avoid rapid renal clearance or leakage through normal vasculature, yet allow EPR-mediated accumulation through tumor-associated leaky vasculature.^[50,51]

Curcumin NPs (Cur-NPs) induce cell apoptosis in CAL27-cisplatin resistance human oral cancer cells

(CAR cells) and inhibit cell growth but possess little cytotoxicity to normal human gingival fibroblasts cells and normal human oral keratinocyte cells. The findings suggest that Cur-NPs trigger apoptotic cell death through regulating the function of MDR1 and the production of reactive oxygen species, and the activation of caspase-9 and caspase-3 connected to intrinsic signaling pathway is the major pharmacologic action of Cur-NPs. Cur-NPs show promise for development as a novel medicine against cisplatin-resistant human oral cancer.^[11]

MMPs (matrix metalloproteinases) are the main prognosticators for metastasis and invasion potential of aggressive malignancies including OSCC. Down-regulation of MMP-2 is a new feature acquired in group treated with dual action DOX-MTX-NPs (Doxorubicin-Methotrexate loaded-NPs) whilst such a potential never reported for free DOX. By affecting the MMP-2 expression in OSCC, DOX-MTX-NP inhibit effectively and specifically progression and invasion of tumoral cells without affecting the normal ones. However, further investigations acquire to clarify the underlying mechanism of action and its further therapeutic potentials in different types of cancer.^[41]

CONCLUSION

Nanotechnology will transform dentistry, healthcare and human life more profoundly than many other developments of the past. Nanotechnology undeniably has a potential to be the most efficient and most favorable form of future treatment and diagnosis of cancer. In the coming years, it will play a key role for early disease detection, diagnostic and therapeutic procedures to improve oral health and general well-being of humankind.

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Conflicts of interest

There are no conflicts of interest.

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